EXHIBIT 2

Expert Report on Benicar (Olmesartan) – General Causation

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Summary of Opinions:

It is my overall judgment, with a high degree of medical certainty, that that there is not a general causation of olmesartan and sprue-like enteropathy. This opinion is rendered as a nationally and internationally known expert in clinical gastroenterology and etiological factors in gastrointestinal diseases, as well as gastrointestinal mucosal immunology and inflammation. I have reviewed the medical literature and applied the standards of evidenced based medicine, the Bradford Hill criteria for assessment of scientific evidence, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The majority of proposed evidence linking olmesartan use to a syndrome of villous atrophy, intestinal inflammation, and diarrhea is an association only, and is based on case series, without any unbiased randomized controlled trials or prospective studies of any type to support a causal relationship. The attempts to put forth a biological mechanism are primarily speculation, and there is only one study that attempted to address mechanism and it is invalidated by very small sample size and lack of paired samples from the same patients, errors of data analysis and presentation, and lack of experimental controls. Thus, there is no biologically plausible mechanism for an association between olmesartan and intestinal injury. The published evidence showing a lack of association is of higher level, and is backed by FDA sentinel reports showing no difference in risk between olmesartan and any other anti-hypertensive agent. Together, these points, discussed in detail below, support my conclusion of lack of biological plausibility and causation.

Statement of Opinions:

I am an expert in clinical gastroenterology, gastrointestinal mucosal immunology and inflammation, and research related to the gastrointestinal tract. My detailed qualifications are below and enumerated in my *Curriculum Vitae*, but it should be noted that highlights include: I hold an endowed chair professorship at Vanderbilt University School of Medicine; I continue to practice in an academic setting as a board-certified gastroenterologist which I have done for 24 years since completion of my gastroenterology fellowship; I run an internationally recognized laboratory and clinical-translational research program related to immunology and inflammation, and serve as the Director of the Vanderbilt Center for Mucosal Inflammation and Cancer; I am an Associate Editor for *Gastroenterology*, the premiere journal in the specialty, where I am the main editor for mucosal immunology and inflammation; and I have served on 38 different National Institutes of Health grant review panels over the past 20 years, primarily focused on gastrointestinal immunology, inflammation and associated carcinogenesis.

For this analysis, I will apply standards of the Oxford Centre for Evidenced Based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

I will examine the most pertinent case studies, reviews, and commentaries, and provide assessments of causation, and provide additional insights related to biological plausibility. I will

also apply the Bradford Hill criteria for assessment of scientific evidence. The Levels of evidence for Therapy/Prevention/Etiology/Harm from the Oxford Centre are delineated as follows in Table 1:

Table 1: Levels of evidence from the Oxford Centre for Evidence-Based Medicine

Level	Description
1a	Systematic Review (with homogeneity) of randomized controlled trials
1b	Individual Randomized Controlled Trial (with narrow confidence interval)
1c	All or None Randomized Controlled Trials (all patients died before Rx available)
2a	Systematic Review (with homogeneity) of Cohort Studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	"Outcomes Research"; Ecological Studies
3a	Systematic Review (with homogeneity) of Case-Control Studies
3b	Individual Case Control Studies
4	Case-Series (and poor quality cohort and case-control studies
5	Expert Opinion, without explicit appraisal, or based on physiology, bench research

My summary opinion is that the majority of purported evidence in the medical literature only proposes an association for olmesartan and gastrointestinal manifestations, and largely constitutes poor quality, Level 4 and Level 5 evidence. In fact, the case-control and cohort studies tend to support a lack of association, and it is mostly the case series and commentaries that propose the association. Further, the level of scientific knowledge to date has not provided a plausible biological mechanism for the proposed association. Most of the attributed causes are pure speculation with very poor evidence.

1) Is there evidence to a reasonable degree of medical certainty that exposure to olmesartan (Benicar) causes a sprue-like enteropathy as first described in Rubio-Tapia et al.[1], the Mayo case series?

Summary of Mayo case series.

This report has been considered the foundational study on the topic of olmesartan-associated enteropathy. It should be noted that this was published in the Mayo Clinic Proceedings, which is the on-site journal produced by the same institution of the authors (except for one co-author from Sweden). Since nearly all members of the Board of Editors are from Mayo Clinic, one can question whether this article was truly peer-reviewed.

This was a descriptive report of a retrospective analysis of 22 cases. It is not a Case Control or Cohort Study; the level of evidence is at best **Level 4** and since it includes a substantial amount of opinion and speculation, it has features of a **Level 5** publication. In the introduction, the authors made reference to a prior study from the same group that reported on a case series of 30 patients with collagenous sprue published in 2010[2], in which they stated in the 2012 paper that one-third of patients from 2010 were using olmesartan. In fact the ratio in the 2010 report[2] was 8 of the 30 patients, which is actually only 27% of patients. In the 2010 study, they only listed the medications and did not link olmesartan to the gastrointestinal issues. Strikingly, the purpose of the 2010 case reports was to emphasize the benefit of gluten free diet and steroids. They primarily suggested use of non-steroidal anti-inflammatory drugs as the cause (in one third of subjects), as well as other medications in 47%.

In the 2012 study[1], the format is a descriptive analysis of the cases. This does not constitute a cohort study, which would have meant that a large group of patients on the medication would have been followed over time. Instead this is an example of disease

manifestation is found and because the disease did not fit with celiac disease, it was linked to the use of olmesartan.

Key points in the case series include:

1) There is no evidence of a dose effect. It is stated that most patients were on the highest dose of 40 mg/day of olmesartan, but no details are given for the individual patients.

2) The duration of exposure was available for 14/22 patients, with the mean duration before diagnosis being 3.1 years; an additional 5 were noted to be on the medicine for at least one year. The implication is that the effect may be idiosyncratic, since there is not the cause and effect reaction seen with most drug allergies.

3) Diarrhea was noted to have been a symptom for a median of 19.2 months so this was generally not a syndrome of rapid onset in the majority of patients.

4) All patients had weight loss at the time of initial presentation.

5) In the 8 patients tested there was profound steatorrhea, with high levels of fat in the stool, a sign of malabsorption.

6) The most commonly used serological test for celiac disease (IgA tissue transglutaminase) was negative in all patients.

7) However, when HLA –DQ typing (genetic testing) was done for celiac disease in 21 of the patients, it was positive in 17/21 (81%). This strongly suggests that some of these patients may have had a genetic predisposition to an autoimmune pathology, and there may not be any type of consistent drug effect.

8) 14/22 patients had anemia. However, surprisingly, they all were listed as having normocytic, normochromic anemia; this is against iron deficiency anemia that one might expect from malabsorption of iron due to villous atrophy, and suggests other etiologies.

9) 10/22 had hypoalbuminemia, indicative of protein loss or malnutrition. However, the other cases did not, suggesting a highly variable case presentation.

10) Small bowel bacterial overgrowth was detected in 12/22 patients. While this could be secondary to a damaged small intestine, it could itself be a cause of damage and could have contributed greatly to the symptoms. This suggests that other factors could have caused disease in these patients and further supports that the olmesartan use is an association and not a pure cause and effect.

11) All 22 patients had small intestinal biopsies showing villous atrophy; there was total atrophy in 15 and partial atrophy in 7 cases. This indicates loss of absorptive epithelium. Evidence of collagen deposition, i.e. collagenous sprue, was seen in 7/22 patients, so this was an inconsistent finding.

12) Small Intestinal inflammation was actually quite variable. Surprisingly, 8/22 had no increase of intra-epithelial lymphocytes, indicative of marked heterogeneity of the case presentations. Further, there was absence of active inflammation (neutrophils) in 7/22, again showing heterogeneity of this syndrome.

13) Colonoscopy was only conducted in 13/22 patients so this crucial information is missing in nearly half of the patients- a further consequence of this being a series of case reports rather than a cohort study in which a standardized work-up would have been expected. In the text of the article it is stated that 5 patients had microscopic colitis presumably meaning there was no endoscopic evidence of disease. However, in Table 2 of the article it is shown that there were actually 7 patients with colitis. This suggests an error in editing, and raises further questions about the precision of this article and the peer review process. Also no follow-up colon biopsies were taken, a marked limitation of the study.

14) It is stated that patients had been previously treated with various therapies without any apparent benefit; most importantly, 20/22 were stated to have been tried on corticosteroids, and that there was no improvement in these cases due to the immunosuppression. Moreover, it is indicated that all patients improved off of olmesartan and did not require any other medications. No patient had any benefit from gluten-free diet.

15) Follow-up duodenal biopsies showed "histologic recovery" in 17/18 patients tested. The fact that not all patients had follow-up biopsies is again indicative that this is a case report series and not a cohort study, where one would expect follow-up to be consistent in all patients. The follow-up time point was highly variable, range of 54-707 days, making these findings hard to interpret regarding the Bradford Hill criteria of cessation of exposure. However, in cases being considered for this litigation, where recovery of histology is very rapid, it may mean that the particular patient is not consistent with the Mayo case series. Also it is important to note that if some of these patients may have actually had other true etiologies, such as seronegative celiac disease, autoimmune enteropathy, other drug effects, occult infections, etc. it would be difficult to know this, because the results of only one follow-up biopsy are described.

16) Gastritis was noted in all 14 patients tested by biopsy. The histology was highly variable with lymphocytic gastritis in 5 patients, collagenous gastritis in 2 patients, and chronic gastritis in 7 patients, with 4 of these showing activity (neutrophils). Thus the gastric presentation is very inconsistent and indicates that this is not a uniform syndrome.

17) In the Discussion the authors expressly state: "We acknowledge that this case series lacks all the information necessary to prove causality but rather reflects an association". Thus there was no presumption of cause and effect.

18) As for rechallenge, two patients reported anecdotally that symptoms worsened with restarting the drug, and two more were noted to have worsening after restarting after hospitalization. However, this is only in 4/22 patients and does not imply replicability of these findings. It is important to realize that such anecdotal histories do not constitute a controlled "rechallenge". Similarly, it is difficult to state that these patients underwent a true "dechallenge" since this article is simply a description of a retrospective clinical case histories and does not include any defined intervention protocol.

19) The authors mention that angiotensin receptor blockers have been suggested to have inhibitory effects on transforming growth factor beta (TGF-ß) and since TGF-ß is importance in gut immune homeostasis, this could be involved, but clearly this is pure speculation, without any data. The metabolism of olmesartan in the intestine from pro-drug to active agent is mentioned, but again this provides no direct mechanistic insight.

–Contrasting information in article by the same Mayo group that shows inconsistencies in the description of the Case Series. This report was from Cartee and Murray in 2014[3]; note that this journal, *Curr Cardiovasc Risk Rep* is not on PubMed so its quality is questionable. This report is a review, with primarily a summary of their Mayo cases and others, and represents **Level 5 Evidence- Expert Opinion**. One discrepancy is that in this article, it is stated: "some more ill patients required budesonide (a topical potent corticosteroid) to initiate a clinical response, control diarrhea, and accelerate healing." Yet in the original report it was stated that all of the 20 patients on steroids had no benefit. Also, it is now stated that 25% and 37% reported improvement in less than 1 week and by 3 weeks, respectively; in the original descriptive report these rapid improvements are not mentioned. Additionally, it is mentioned that several of the original patients likely had underlying celiac disease, manifested as recurrence of symptoms with resumption of gluten in the diet. No details of the number of patients with this presentation are given, but the original article claimed that lack of clinical response to gluten exclusion was a hallmark of the olmesartan-associated enteropathy. So this is a crucial inconsistency that further weakens the original case series. Further, in this follow-up article the proposed mechanism of an effect on TGF-ß and resulting immune dysregulation is again mentioned; but now it is pointed out that TGF-ß is important in driving collagen deposition during inflammation, which was common in the cases from the Mayo Clinic. Thus, suppression of TGF-ß function would be inconsistent with TGF-ß-dependent collagen synthesis. So essentially, the authors have already disavowed the prior hypothesis, and this is all pure speculation. In fact the authors state it is also made clear that there needs to be a "search for a mechanism(s)".

The discussion clearly states: "Once the association is recognized and the drug stopped, the disorder resolves". If this were truly the case, according to Bradford Hill criteria this would fit the concept of cessation of exposure, and should be consistent between cases in the Mayo series and in the other case reports. However, in the actual cases under consideration, a variety of complaints are attributed to the olmesartan years after the exposure was terminated.

Key points from other case series.

–Theophile et al., *Dig Liver Dis*, 2014[4], described 5 cases from Bordeaux, France of sprue-like enteropathy in patients on olmesartan. Here, 4/5 showed some degree of villous atrophy, but one did not. 2/5 patients had reintroduction of olmesartan and both had recurrent symptoms. This case series is also **Level 4 Evidence** as it is highly descriptive and anecdotal. The discussion mentions the French pharmacovigilance database had 28 patients with diarrhea on olmesartan but mentions that only two of these had villous atrophy. Thus, the quality of this additional information is of very limited relevance.

–Marthey et al. 2014[5] reported on cases from France. The method was again a series of case reports and not a cohort or case-control study, making it **Level 4 Evidence**. A total of 36 patients were listed of which 32/36 had villous atrophy. 14/15 patients responded to steroids, which is different from the original Mayo case series report. 9/10 patients with reintroduction of olmesartan had relapses. This would suggest that actual cases under consideration are unlikely to have olmesartan-induced gastrointestinal disorders if symptoms do not recur with resumption of olmesartan. In this French case series, 11/18 were HLA DQ2 or DQ8 positive, again suggesting a genetic basis for this disorder and that the syndrome is not due to a simple cause and effect. 9/14 patients responded to corticosteroids, and 14/15 had remission with corticosteroids and/or other immunosuppresants, without withdrawal of the olmesartan, as the association was not suspected. Thus, the concept from the original Mayo case series that the drug must be withdrawn for resolution is not a consistent finding.

Based on my review of the above case reports, including case reports or series published after the original Mayo Clinic case series, my opinion is that within a reasonable degree of medical certainty, these reports do not provide evidence of general causation.

Specifically, these publications are Level 4 to Level 5 reports based on descriptions of patients who were on olmesartan, where there was only an association with diarrhea and small intestinal villous atrophy. There was marked variability in these patients with some showing an immunological basis due to positive HLA DQ2 and DQ8 that are markers associated with celiac disease and some not; some showing small intestinal inflammation, but some not; some showing colitis or gastritis in addition to the small intestinal inflammation, but some not. Importantly, the Mayo Clinic patients were originally reported to have been refractory to steroid therapy and to have a slow recovery, but in a subsequent report the exact same patients were stated to frequently respond to steroids and have a fast recovery off of the olmesartan; these obvious inconsistencies indicate that the level of evidence is in the 4-5 range on the 5-point scale and is often anecdotal.

While alternative explanations are not clear, it should be noted that an autoimmune basis or other unknown cause may be equally likely. For example, Brown et al.[6] reported in 2011 a case series from Australia of 18 patients who had abrupt onset of celiac-like enteropathy that was self-limited. These cases were collected prospectively. Celiac disease was excluded by negative tissue transglutaminase and HLA DQ2/DQ8 genotyping. 15/18 had diarrhea and 11/18 had vomiting. All had a lymphoplasmacytic infiltrate on the duodenal biopsies, and 9/18 had neutrophilic infiltration. 2/8 patients tested had colonic lymphocytosis, 4/10 patients tested had gastric abnormalities. It was stated that medications, immune deficiency, or parasitic infection

were excluded. It was suggested that viral etiology or another foreign antigen were the most likely causes[6]. In the Discussion, the authors indicated that enteric viral infections can cause a celiac-like inflammatory response in the small intestine, citing a 2009 review in the prestigious *New England Journal of Medicine*[7] that described that in volunteers given norovirus, the small intestinal pathology showed villous blunting, and infiltration of neutrophils and mononuclear cells, which is very similar to what is described in the acute self-limited celiac-like enteropathy study[6] and in the cases associated with olmesartan exposure.

2. Additional information, derived from other studies, which is relevant to the question of general causation.

–The ROADMAP study[8] that was being conducted to assess effects of olmesartan (40 mg/day) on complications of type 2 diabetes. 2232 patients were on drug and 2215 on placebo, for a median of 3.2 years. After the Mayo report of olmesartan-associated enteropathy, the authors of the ROADMAP study reviewed all the intestinal symptom-related adverse events[8]. They reported that there were no differences between drug and placebo for any intestinal adverse events. The rate of diarrhea was 2.3% in both groups and there were no differences in gastroenteritis, colitis (actually there 6 cases in placebo and only 1 in olmesartan) and no differences in abdominal pain, nausea, vomiting, fatigue, or weight loss. Thus, in a prospective study that was a randomized controlled trial of 4447 patients, there was no difference in gastrointestinal effects over a long period of follow-up in patients on olmesartan versus placebo. Since this was not the primary endpoint of the study, one could downgrade the quality of evidence from Level 1b to **Level 2b**, but it is still higher quality than a case series.

–Degaetani et al. (2013)[9] performed a retrospective review of 72 patients with villous atrophy and negative celiac serology found over a 10-year period from a single center, Columbia University Medical Center in New York, NY. In this case series **(Level 4 evidence)**, 16/72 patients were noted to have villous atrophy linked to olmesartan use. However, seronegative celiac disease was present in 20/72 (28%), and other disease etiologies included: unspecified (14%), common variable immunodeficiency (6%), autoimmune enteropathy (4%), giardia infection (4%), lymphoma (5%), tropical sprue (4%), collagenous sprue (3%), bacterial overgrowth (3%), Crohn's disease (1%), and extrinsic gastric metaplasia (1%). Thus, olmesartan was only put forth as the potential etiology in 22% of these already unusual cases.

Furthermore, the HLA DQ2/8 was positive in 70% of the cases. Amongst the olmesartan-exposed patients, 13/14 (93%) of those tested were positive. This, even more strikingly than the Mayo case series where 81% tested were positive, strongly implicates an immune-related predisposition, and suggests that individual cases in this litigation where the HLA status is negative may not have the true syndrome. Also notable was that 16/16 patients on olmesartan were noted in Table 3 in the Degaetani study[9] to have clinical improvement with immunosuppression, which is different from the original Mayo case series report that indicated that no patients had improvement with immunosuppression. This point is a major source of confusion, especially since the follow-up report that was an opinion article (Level 5) from the Mayo group reversed the original statements and indicated some patients responded to corticosteroids.

–Greywood et al. (2014)[10] conducted a case-control study of all outpatients undergoing EGD or colonoscopy over age 50 from January 1, 2007 to March 31, 2013 at Columbia University Medical Center in New York, NY. Cases were defined as those where the endoscopic examination was performed for diarrhea and the controls were those undergoing EGD for esophageal reflux, or colonoscopy for colorectal cancer screening. The authors identified 2088 EGDs and 12,428 colonoscopies meeting the inclusion criteria. There was not a statistically

significant association between olmesartan and diarrhea in patients who had EGD or colonoscopy. There was also no association between olmesartan and any histologic diagnoses of celiac disease or microscopic colitis. In total, there were 393 patients with diarrhea in the EGD group (19%) and 867 patients in the colonoscopy group (7%). Olmesartan use was in 22/2088 of the EGD group and 83/12,428 colonoscopy group. Importantly, both univariate and multivariate analyses showed no relationship between olmesartan and diarrhea or histologic features of celiac disease or microscopic colitis. It should be noted that in this study there was a standardized, in person assessment of medication use by a trained nurse preceding each endoscopic procedure. While the study was retrospective, it was large, and was a case-control study, constituting **Level 3b Evidence.**

–Lagana et al. (2015)[11] conductive a retrospective cohort study at Columbia University Medical Center, New York, NY of patients with abdominal pain undergoing EGD who were taking ARBs. Of these, 20 were documented to be taking olmesartan by a trained nurse in a face-to-face interview at the time of endoscopy. The 20 age- and sex-matched controls were not taking olmesartan or other ARBs. Patients with known celiac disease, IBD, or *H. pylori* infection were excluded. The main finding of this study was that the olmesartan users had no increase in any histopathologic findings on the duodenal biopsies. Despite this, the authors stated: "there were variables and a composite outcome which showed trends towards significance". It is very important to note that such statements are unscientific. Moreover, the olmesartan value for the presence of any sprue-like features was actually lower than the control group for the other ARB users (12/20 positive). This suggests large differences in the control groups. Also the frequency of 10/20 positive with olmesartan was essentially identical to the other ARB users group (9/10 positive). Similarly, the other value with a "trend" was the mean maximum IEL count that was also not significantly increased by the statistical testing, and the value was again nearly identical to the other ARB users, and again lower than the level for the ARB matched controls. In my experience as an Associate Editor for *Gastroenterology*, *BMC Gastroenterology*, and *Oncogene*, and as a reviewer for over 60 journals, I can state unequivocally that if I received a manuscript to handle as editor with the absence of any statistically significant data and reference only to "trends", and had such substantial differences between control groups, I would reject the manuscript without sending it out for additional peer review; if I received this manuscript as a reviewer, I would immediately reject it. Another issue is that the authors refer to a posthoc analysis, which was a secondary analysis where only one histologic sprue-like feature may have been present, which is of limited validity since this analysis was not part of the original study design and was not the primary endpoint. Thus, the final conclusion for this study is that while technically it could be considered **Level 2b Evidence** as it was from a retrospective cohort study, in fact the quality of the study was poor due to being underpowered, it is clearly a negative study, and it has no validity to support a conclusion of any association of olmesartan with histologic changes.

–Basson et al. (2015)[12] reported on a nationwide cohort from France, in which hospitalization for intestinal malabsorption was determined. This is a retrospective cohort study (**Level 2b Evidence**). However, the level of evidence is greatly diminished because no intestinal biopsy data was available for the study. The authors reported an increased adjusted rate of admissions for malabsorption for olmesartan versus ACE inhibitors. However, it is very important to note that the incidence rate was only 5.6 per 100,000 person years for olmesartan versus 2.4 in the ACE inhibitor group and 1.8 in the other ARB group. Also, the authors point out that the study was based on administrative data and there was no comparison with actual chart review data. The overall number needed to harm of 31,350 patient years of olmesartan exposure should also be noted, indicative of hospitalization for malabsorption being rare.

–The FDA Mini-Sentinel Report covering the period of January 1, 2007 to December 31, 2011 included the data for "celiac disease events" for olmesartan and other ARBs and a selection of other anti-hypertensives. There were no differences in cases per million days at risk when compared to any of the other agents (Figure 1bv).

-Padwal et al. (2014)[13] conducted a population-based retrospective cohort study using a large US claims database to compare users of olmesartan and other ARBs. The patients in the database were all diabetic ARB users. There were 45,185 cases that included 10,370 olmesartan users. There were a total of 116,721 patient years. Compared to other ARBs, there were no differences in all cause hospitalization or all-cause mortality, and no differences in gastrointestinal disease-related hospitalizations. This is **Level 2b Evidence**.

–Summary review of these data from studies that go beyond simple case series provides evidence that the evidence for an association between olmesartan and enteropathy is insufficient.

Specifically, there were two positive studies. In the DeGaetani case series[9], of 72 patients in a single center (Columbia University Medical Center) with villous atrophy and negative celiac serology, disease was attributed to olmesartan in 16 patients (22%), but it should be noted that this is a referral center for celiac disease and this collection of cases took 10 years to accrue. Also, there were two completely negative studies from the same medical center (Greywood[10] and Lagana[11]). Further, the 100% response to corticosteroids differs drastically from the original Mayo case series raising substantial doubts about the nature of the purported syndrome. Second, the Basson study[12] showed a difference in hospitalizations in France for malabsorption for olmesartan users versus other ARBs or ACE inhibitors, but the difference was only about 3 per 100,000 person years and the overall incidence was very low.

In contrast, I have listed multiple examples of negative associations for olmesartan. The ROADMAP study[8] showed no increased risk of gastrointestinal events in a study of nearly 4500 patients. Similarly, the Padwal population-based study[13], which included over 10,000 olmesartan users, showed no differences in gastrointestinal complications resulting in hospitalizations. In the Greywood case-control study[10] there was no association of olmesartan use with diarrhea or with histologic features of celiac disease or colitis; this was in a large study of over 2,000 EGDs and over 12,000 colonoscopies being conducted for diarrhea, with 105 patients on olmesartan. In the Lagana study[11] there was no association of olmesartan in a case-control study compared to other ARBs in terms of histologic evidence of duodenal damage. Finally, the FDA Mini-Sentinel report showed no difference between olmesartan and any other anti-hypertensive in terms of celiac-like disease presentation.

–Another substantial gap in knowledge is any potential biological mechanism as to how olmesartan could cause intestinal injury and inflammation that mimics celiac disease. To this end, the Mayo Clinic group conducted studies to attempt to investigate this, in Marietta et al. (2015)[14]. This study used duodenal biopsies obtained on and off of olmesartan. The study had multiple obvious design flaws. 1) There were 11 patients before and 17 patients after olmesartan; the uneven number reflects the likelihood that all samples were obtained from pathology archives retrospectively. 2) There are reported to be 7 matched pairs only; the rest were from unmatched cases, reducing the power. In fact, in none of the analyses are the specific 7 paired cases even analyzed or presented. The time off of olmesartan was not standardized due to the retrospective nature of the study. 3) In the methods it is stated that for the immunohistochemistry studies the differences in staining scores were assessed using the nonparametric Mann-Whitney rank sum-test, which is appropriate for comparing two groups were the data are not normally distributed. However, in each of the legends for Figures 1-5, it is stated that the unpaired *t*-test was performed. This is important because the majority of the data

appears to be not normally distributed, so the test appears to be erroneous. 4) The number of cases used in the Figures 1-5 varies considerably. The number of cases shown in Figure 2 is only 10 and 7 and in Figure 5 is only 10 and 5, compared to the other figures.

In terms of the data in Figure 1, the authors show increased CD8+ cells, but no increase in CD4+ cells in olmesartan "on" versus "off" samples. The lack of increased T helper cells (CD4+) is somewhat surprising, given that these cells lead to inflammation in intestinal inflammatory states through the Th1 and Th17 pathways. When Figure 2 is discussed, the authors state that there is an increase in granzyme B, indicative of cytotoxic T cells in the "on" versus "off" biopsies. However, these data are not statistically significant, so this claim cannot be made. Yet despite this, they restate this false association in the Discussion. In Figure 3 there is increased staining for FoxP3, a marker of regulatory T cells (Tregs), in the "on" versus "off" biopsies. Since they were increased, the authors state that this indicates that the FoxP3+ cells were present and actually increased, but were not able to suppress inflammation. This is pure speculation. To get a better grasp on the situation, flow cytometry with T cell markers for Tregs should be tested, but since this study is retrospective and conducted on archival tissues only, this cannot be done, which is a major weakness. The authors used intracellular staining for phosphorylated SMAD 2/3 as a marker of TGF-ß signaling. They found that this was increased in the "on" versus "off" biopsies, which was interpreted as indicating that TGF-ß signaling was active. This directly opposes the proposed mechanism of olmesartan-induced inflammation that was speculated in the original 2012 Mayo case series of presumed diminished TGF-ß activation.

Because celiac disease patients have overexpression of the cytokine IL-15 and its receptor IL-15R, and this signaling has been linked to activation of cytotoxic T cells and epithelial cell destruction, the authors pursued this possibility in the olmesartan cases. The authors indicate that IL-15R staining was not different in immune cells of the lamina propria, but is increased in the intestinal epithelium of the "on" versus "off" biopsies. These data are greatly weakened by the inclusion of only 5 off cases to go with the 10 on cases. 3 of the "off" cases overlap with "on" cases in terms of their staining scores, making the conclusion of significance highly unlikely. Further, the epithelial staining in the "on" case shown may represent mostly artifact, because the tissue exhibits a loss of the normal epithelial architecture, which can contribute to non-specific staining; controls without the primary antibody should have been done on the olmesartan "on" cases. Also the IL-15 levels were not assessed.

In an effort to provide additional data the authors utilized an epithelial cell line to assess a potential mechanism. It should be noted that the Caco-2 cells selected are a colon cancer cell line that has limited relevance to the small intestine, the site of the enteropathy to be studied. The cells were treated in vitro with olmesartan and two other ARBs, losartan and telmisartan. The dose used is unclear, because in the legend to Figure 6 it is stated that the does was 30 micromolar, but in the text it is written two separated times that the dose was 30 millimolar a difference of 1000-fold (presumably this is an editing error and it is really micromolar). Regardless, the rational for this dose is unexplained and the relationship to human dosing of 40 mg/day is not calculated. There is no dose response, a basic expectation in such studies. These studies do not have the proper control of cells treated with the vehicle alone (DMSO). This is important because DMSO itself can be toxic. Also the potential cytotoxicity of the ARBs was not measured by a cell viability assay. The staining in Figure 6A for IL-15 is difficult to accept given that all cells are positive, suggesting overstaining. Use of a known positive control for comparison would have been useful. Figure 6D and 6E are staining for IL-15R, but strangely, no staining for olmesartan is shown, which is very odd since this is the purpose of the study. In Figure 7 and 8 alterations in tight junctions are shown by staining for the marker ZO-1. Such staining was not quantified and also should have been corroborated with functional studies, such as trans-epithelial electrical resistance.

Taken together, the great limitations in study design where none of the paired biopsies were shown, the small number of cases, the errors in statistical analysis and interpretation, the

lack of staining and experimental controls, the lack of dose response, appropriate controls, and functional correlations in the in vitro data are all indicative of major issues with the study. Thus, I conclude that this study does not provide a plausible biological mechanism.

However, in the expert report from Dr. Tackett, he states on page 8 that "peer reviewed literature has elucidated the plausible biological mechanism by which olmesartan causes enteropathy". He restates the proposed findings of the Marietta study. He does not consider that none of the analyses were actually done on the paired biopsy samples from the same patients "on and "off" the medication. He states that there is an increase in CD8+ cells without mentioning the lack of difference in the CD4+ cells and states that there was an increase in the granzyme B+ cells even though those data were not statistically significant. The increased Foxp3+ cells being increased with a simple restatement of the Marietta argument that this must mean that they are functional, but the actual activity of the Foxp3+ cells or even the assurance that the staining came from T cells was never tested. He also restates the staining results for IL-15R, which I above indicated were of dubious quality and limited to only 5 cases in the "off" group making the stated significance very dubious. The in vitro data is simply restated, but I have already indicated that these experiments lacked appropriate controls, dose response studies, cytotoxicity assessments, and functional correlations. Thus, I dispute the comment from Dr. Tackett that the Marietta study provides any believable biological mechanisms.

Dr. Tackett also discusses two animal studies that suggest potential anti-inflammatory effects of olmesartan in the gut, Nagib et al[15] and de Araujo et al[16]. He dismisses the findings based on the idea that the dosing was too high. He calculates that the human dosing of 40 mg/day is 0.57 mg/kg, which is lower than some of the doses of 5 and 10 mg/kg used in the rodent studies. However, Dr. Tackett neglected to factor in that the metabolic rate of rodents is far greater than that of humans so that drugs are typically metabolized much faster, and it is quite standard to use dosing of 10-fold higher or more in mice and rats. Additionally Dr. Tackett expresses concern about the findings in the de Araujo study from a Brazilian group that while the rats gained histologic improvement in a methotrexate small intestinal injury model when on olmesartan, some experienced weight loss and diarrhea. I have reviewed this paper and found it to be of limited quality, particularly since it is in a lower tier journal (Biological and Pharmaceutical Bulletin, impact factor 1.8) and any attempts to extrapolate from this secondary finding, when the main finding was protection from histologic injury, is an over-interpretation of the findings. Additionally, it should be noted that there is another paper by the same Brazilian group showing benefit of olmesartan in the same rat methotrexate model without any side effects of olmesartan that was published in a better journal (PLOS One, impact factor 3.2) [17]. Moreover, it should be noted that the study by Nagib[15] demonstrated reduction of colitis in rats induced by dextran sodium sulfate that exceeded the benefit of sulfasalazine, which was used as a reference drug. Also, Fatima et al.[18] reported beneficial effects of olmesartan in a rat acetic acid colitis model. In neither of the later two studies were any side effects of olmesartan noted.

There are also rodent studies showing beneficial effects of olmesartan in other animal models. This includes: 1) Sipal et al.[19], preventing liver fibrosis in diabetic rats that was less apparent with losartan and valsataran; 2) Seko[20], preventing myocardial inflammation in a coxsackievirus model; 3) Wu et al.[21], improving experimental heart failure by enhancing cardiac remodeling. None of these studies reported any gastrointestinal side effects.

I will now discuss the most up to date **Bradford Hill** criteria for causation as enumerated in Schunemann et al.[22] that is based on the Grading of Recommendations Assessment, Development and Evaluation (**GRADE**) approach[23].

1) Strength of association. Most of the data suggesting the association between olmesartan and enteropathy derives from Level 4 or Level 5 Evidence. There is only one study with a higher level of evidence, but this Basson study[12] is based on administrative data, which

was reviewed retrospectively. In contrast there are multiple cohort and case-control studies, which include four Level 2 and one Level 3 study that all show no association. Thus, with the bias of simply collecting cases there appears to be an association, but with higher-level studies with an unbiased approach, there is no association. This leads to the conclusion that the association is very weak, if it exists at all.

2) Consistency. Even the case series show a remarkable amount of inconsistency. Patient presentations are highly variable, with some cases showing acute onset and others years of exposure. There are also inconsistencies about the involvement of the stomach and the colon in the disease process. Some series report 100% response to immunosuppression (DeGaetani[9]) and others report no response to immunosuppression (Rubio-Tapia[1]). In contrast, the cohort and case-control studies show a consistent lack of association.

3) Temporality or study design suitability. The positive data for olmesartan enteropathy comes entirely from observational studies- i.e. case reports. This is considered the weakest level of evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)[22]. These case series heavily rely on the assumption that exposure to the drug before developing symptoms and improvement off of drug constitutes evidence of temporality. However, these studies are merely descriptive. Furthermore, the time period of onset of symptoms following exposure is highly variable as reported in the case series literature. In fact, there are no prospective studies on olmesartan users and gastrointestinal complications. In the case control and cohort studies patients are generally followed for specific periods of time, but assessed retrospectively. None of these studies have borne out a relationship between olmesartan and gastrointestinal symptoms or histologic damage.

4) Biological gradient. This would mean a gradient between an exposure and the magnitude of an effect, i.e. a dose response wherein an increased dose would cause an increased risk of the adverse event, or a more severe course. There is no evidence of this whatsoever related to olmesartan. In the original Mayo case series[1] it was stated that most patients were on the maximal dose of olmesartan of 40 mg/day. The other studies did not address dosing. Thus, there is no evidence to support a biological gradient.

5) Specificity. Causation is deemed more likely if there is a specific outcome from a specific exposure. The simplistic outcome was purported to be sprue-like enteropathy. But in actual fact, in the Mayo case series there was marked variability with cases showing variable extent of villous atrophy and variable types of inflammatory infiltrates (neutrophilic vs. lymphocytic) on the histologic assessments. There was no specificity related to the nature of the colonic inflammation, which was highly variable in frequency and type in the various case reports. The presence of the HLA DQ2/DQ8 association is not completely consistent, but it is a suggestion of a genetic and immunologic basis, but does not provide any specific mechanism, since it is simply genotyping. In addition, as enumerated in Aziz[24] and Degaetani[9] there are numerous other potential causes of sprue-like enteropathy besides medication-associated syndromes. The recent study by Aziz et al. (2016)[24] demonstrates the wide array of diseases associated with seronegative villous atrophy. Examining 200 patients over a 15-year period, seronegative celiac disease explained 62 (31%) of cases. Of the remaining 138 patients (69%) the main causes were infection in 54 (27%), inflammatory/immune-mediated disorders in 35 (17.5%). Drugs were the cause in 13 (6.5%) with two cases related to ARBs (type not specified). An additional 36 (18%) had no cause found and 26 of these (72%) spontaneously resolved.

6) Biological plausibility. Whether the association is plausible is important for causation in the Bradford Hill criteria. In GRADE, the evaluation of biological markers can be

used to assess disease status such as viral load or CD4 count in HIV patients[22]. In the olmesartan-associated enteropathy, there is currently no quality evidence of a biological mechanism. There is speculation of alterations in TGF-ß-driven immunoregulation or increased apoptosis. But neither of these speculations have been demonstrated; the TGF-ß hypothesis was refuted by Murray's own group when they failed in the Marietta paper to show any differences in signaling downstream of TGF-ß in biopsies from patients on olmesartan versus off olmesartan. Il-15 expression has also been put forward but the evidence is weak, and a single cytokine is highly unlikely to explain an entire syndrome. The deficiencies in the Marietta et al. study are enumerated above. Additionally, the summary opinion of Dr. Tackett is also discussed above, and my opinion is that Dr. Tackett has restated the conclusions of the low-level evidence case series and the highly flawed Marietta paper in assuming biological plausibility. Again, my summary opinion is that there is no biological plausible mechanism.

7) Coherence. Causation is more likely if what is observed is supported by, and in agreement with the natural history of the disease. This is very difficult to assess since the natural history of this supposed disease derives only from case series that exhibit substantial variability between the studies. However, if the concept of natural history can be applied to a proposed drug-induced disease process, it is apparent that there is marked variability in the gastrointestinal disease association. This leads to uncertainty as to what the disease actually consists of. The following questions are completely unanswered due to the low quality of evidence of case series. Does the proposed syndrome include gastric and colonic inflammation in addition to small intestinal enteropathy? Does it include an immunologic predisposition, so that HLA DQ2 and DQ8 negativity protects from this disease process and makes individual cases with negative HLA typing more unlikely to fit the purported syndrome? Does response to immunosuppression help rule in or rule out the disease since the case reports are conflicting?

There are other important considerations. There is a long lag time between initiation of olmesartan and the development of symptoms. The reports suggest that the course of improvement with dechallenge is highly variable. Furthermore, the extreme rarity of the event compared to the very large number of patients on the medication is difficult to explain.

8) Experimental evidence. GRADE places a focus on the level of evidence[22]. As listed above, there are no randomized control trials to provide experimental evidence. There are no animal data showing any cause and effect of olmesartan and intestinal injury. The case-control and cohort studies do not show any association. It is only the Level 4 and Level 5 case studies, reviews, and commentaries that provide the literature on association, which is not hard experimental evidence.

9) Reasoning by analogy. Bradford Hill indicates that similar associations would support causation. There are other examples of drug-induced gastrointestinal injury. The prototype drug class is non-steroidal anti-inflammatory drugs (NSAIDs). The literature linking NSAIDs to an array of gastrointestinal complications is enormous. In stark contrast, the literature for olmesartan is extremely limited and not robust. Considering the concept that by analogy, other drugs with a very similar mode of action, i.e. other ARBs, should have the same effect as olmesartan. However this does not appear to be the case. In the case control Lagana study[11] of patients undergoing duodenal biopsy, the authors showed that there was no association of non-olmesartan ARBs with sprue-like histology. There are only a few case reports of a single patient on other ARBs with similar sprue-like disease, which is especially low quality evidence. Together, this information suggests that the criteria of reasoning by analogy are not met.

3) General considerations related to clinical presentations of diarrhea, enteritis, and colitis in adults.

Acute diarrhea is defined as symptoms lasting 14 days or less. Most cases of acute diarrhea in adults in resource-rich settings like the USA can be attributed to an infectious cause. A crucial part of the evaluation of a patient with diarrhea is to make efforts to distinguish diarrhea from infectious causes from that due to other causes. In assessing a patient with acute diarrhea, it is important to assess the duration, frequency, and characteristics of the symptoms, including the presence of fever, blood or mucus in the stool, and abdominal pain; to assess the patient's volume status, i.e. determine if dehydration is present; and to evaluate for other comorbidities. In hospitalized patients with diarrhea, routine stool bacterial culture is of low yield. Thus, it is standard to also send stool for *C. difficile* testing and consider empiric initial treatment for this infection if the clinical suspicion is high, as in antecedent exposure to antibiotics or prior history of *C. difficile* infection.

If the patient has bloody diarrhea or fever, then stool bacterial cultures, and specific testing for toxigenic *E. coli* (type 0157:H7) is particularly warranted. Testing for parasites and *C. difficile* is also needed. Management may include empiric antibiotics in addition to rehydration and anti-diarrheals (such as bismuth and/or loperamide). If the disease is less severe and there is no fever, empiric antibiotics are generally not utilized, pending culture results.

If the patient does not have bloody diarrhea, other signs should be considered, including severity of illness (hypovolemia, more than 6 loose stools/24 hours, abdominal pain, requirement for hospitalization), fever, old age (greater than 70), important co-morbidities (cardiac disease, immunocompromised host, pregnancy), symptoms lasting more than one week, or public health concerns. If any of these are present, this will also guide the need for stool cultures and for empiric antibiotics.

Another important consideration is that invasive diarrhea, i.e. dysentery, is characterized by visible blood and mucus. This is usually associated with fever and abdominal pain. In contrast, watery diarrhea typically lacks these features.

Major causes of acute diarrhea include viruses (norovirus, rotavirus, adenoviruses, astrovirus, etc.), bacteria (*Salmonella*, *Campylobacter*, *Shigella*, enterotoxigenic *E. coli*, *C. difficile*) and parasites/protozoa (*Cryptosporidium*, *Giardia*, *Cyclospora*, *Entamoeba*, etc.). Most cases of acute infectious diarrhea are viral as stool cultures are only positive in about 1 to 5 percent of cases. Exposure to tainted food is a common cause of infectious diarrhea, as well as exposure to animals (*Salmonella*) and travel to resource-limited settings.

Persistent diarrhea is defined as symptoms for more than 14 and less than 30 days, and chronic diarrhea indicates disease for more than 30 days. The array of potential causes for chronic diarrhea is great. These include irritable bowel syndrome and functional diarrhea, which do not include weight loss, anemia, occult or obvious gastrointestinal bleeding, or nocturnal awakening with pain or diarrhea. Additionally, inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis must be considered. IBD can have highly variable presentations, but is typically associated with bloody diarrhea and/or fever, weight loss, defecatory urgency, and/or abdominal pain. However, it is important to note that IBD in more mild forms can present with an absence of physical examination findings and a lack of severe manifestations such as anemia. Microscopic colitis indicates the presence of histologic colonic inflammation associated with watery diarrhea without overt bleeding. This is typically linked to the histologic abnormalities of lymphocytic colitis and collagenous colitis in which collagen bands are deposited in the subepithelial mucosa.

Malabsorptive syndromes: Malabsorption is impaired absorption (uptake) of nutrients in the small intestine. This can include primary malabsorption from congenital defects in the intestinal epithelial transport systems. More commonly, it is secondary malabsorption from small intestinal Crohn's disease, celiac disease, or surgical resections that alter the epithelial surface

where nutrients enter the body. There can also be impaired digestion within the intestinal lumen such as with exocrine pancreatic insufficiency, leading to fat malabsorption and diarrhea, or as with lactose maldigestion due to lactase deficiency. Thus, very common causes are lactose intolerance, chronic pancreatitis, celiac disease, and bacterial overgrowth of the small intestine. Chronic infections can also be a cause, such as *C. difficile*, *Aeromonas*, *Campylobacter*, *Giardia*, *Amebae*, *Cryptosporidium*, *Cyclospora*, and Whipple's disease (due to the bacterium *Tropheryma whipplei*).

Many medications have been linked to diarrhea; the list is very extensive and can include: antiarrhythmics (e.g. digoxin, procainamide, quinidine); other antihypertensives (ACE inhibitors, Beta-blockers, hydralazine); cholesterol-lowering agents (cholestyramine, clofibrate, gemfibrozil, statins); diuretics; central nervous system-associated agents such as antianxiety drugs, anti-Parkinson's drugs, and psychiatric medications; the oral hypoglycemic agents, especially metformin; thyroid replacement, such as synthroid; GI antiulcer and antacid drugs, namely H2 receptor blockers, proton pump inhibitors, misoprostol, and magnesium containing antacids; non steroidal anti-inflammatory drugs (NSAIDs), treatments for gout such as colchicine; antibiotics; antineoplastic agents; vitamins/supplements, such as magnesium and vitamin C; and dietary exposure to alcohol and sugary substitutes, especially sorbitol.

It should be noted that in two individual cases in this litigation that I have reviewed concurrent medication-related exposures have included: ACE inhibitors, Beta blockers, hydralazine, statins, diuretics, antianxiety and sleeping aids; thyroid replacement, proton pump inhibitors; treatment for gout, NSAIDs, and heavy alcohol intake (in one case). Thus, the watery diarrhea in the cases under investigation could have been linked to any of these agents.

As was central to the patients in the Case Series discussed above, biopsy of the small intestine and the colon are essential in the work-up of chronic diarrhea. There are many potential explanations for the syndrome of villous atrophy without serologic evidence of celiac disease. The recent study by Aziz et al. (2016)[24] demonstrates the wide array of diseases associated with seronegative villous atrophy. As discussed above, in 200 patients studied, seronegative celiac disease explained 62 (31%) of cases. Of the remaining 138 patients (69%) the main causes were infection in 54 (27%) and inflammatory/immune-mediated disorders in 35 (17.5%). Drugs were the cause in 13 (6.5%) and an additional 36 (18%) had no cause found and 26 of these 36 cases (72%) spontaneously resolved. Also as discussed above, Degaetani et al. (2013)[9] performed a retrospective review of patients with villous atrophy and negative celiac serology and found frequent presentations of seronegative celiac disease (28%), and other disease etiologies included: unspecified (14%), common variable immunodeficiency (6%), autoimmune enteropathy (4%), *Giardia* infection (4%), lymphoma (5%), tropical sprue (4%), collagenous sprue (3%), bacterial overgrowth (3%), Crohn's disease (1%), and extrinsic gastric metaplasia (1%).

Taken together, the work-up of diarrhea as a presenting condition is based largely on whether the presentation is acute or chronic. One common theme in the two cases under litigation that I reviewed was that the patients presented with diarrhea that initially seemed to be acute, so that they were tested for bacterial infection and treated empirically with antibiotics; the disease became persistent, necessitating hospitalization, but resolved within a few weeks so that the transition to a true chronic state did not develop. Since both patients I reviewed were treated with corticosteroids, and gained apparent benefit from these agents, this is against the olmesartan enteropathy of the Mayo Clinic case series. Case reviews of patients with seronegative celiac disease include a substantial percentage of patients with unspecified or no cause found, and importantly the other potential causes such as autoimmune enteritis and small bowel bacterial overgrowth were not considered in the cases I reviewed. This coupled with the many other potentially offending medications that the patients were exposed to, make it very unlikely that the olmesartan can be considered the etiology for the gastrointestinal complaints within a reasonable degree of medical certainty.

QUALIFICATIONS: Please see my full *Curriculum Vitae* for details.

Education: I graduated from the College of Arts and Sciences at Cornell University in Ithaca, NY in 1982 with B.A. degree. I was a College Scholar, Magna Cum Laude Honors Graduate, and was inducted into Phi Beta Kappa. I then graduated from Harvard Medical School in 1986, receiving the degree of M.D. I undertook a three-year residency in Internal Medicine at Case Western Reserve University School of Medicine in Cleveland, OH, graduating in 1989. I then completed a fellowship in Gastroenterology at The University of Chicago Medical Center in Chicago, IL, graduating in 1993. This was a three-year program, which I extended to four years as I was conducting laboratory research that was supported by a research grant that I had obtained from the Crohn's & Colitis Foundation of America (CCFA).

American Board of Internal Medicine (ABIM) Certification and Licensure: I obtained lifetime certification in Internal Medicine in 1989. I obtained certification in Gastroenterology in 1993, and have successfully recertified through the ABIM by written examination in 2003 and 2013; I am currently certified until 2023. I have held medical licenses in Illinois, Maryland, and Tennessee; my current active license is in Tennessee.

Academic History: After completing fellowship I began a tenure-track Assistant Professor position as a physician-scientist at the University of Maryland School of Medicine in Baltimore, MD, in 1993. I directed an independent, laboratory-based research program and practiced Gastroenterology at both the Baltimore Veterans Affairs Medical Center and the University of Maryland Medical Center. I was promoted to Associate Professor of Medicine in 2000 and received tenure in 2002. From 2002 until 2005 I served as the Chief of Gastroenterology at the Veteran Affairs Maryland Healthcare System.

In 2005, I was recruited to Vanderbilt University School of Medicine in Nashville, TN as Professor of Medicine. That same year I was appointed as Professor of Cancer Biology. In 2011, I was appointed Professor of Pathology, Microbiology and Immunology. In 2012 I was honored with the Thomas F. Frist Sr. Chair in Medicine, an endowed professorship. From 2005 to 2015 I served as the Gastroenterology Fellowship Program Director, where I was responsible for all aspects of the training program for physicians that have completed residency in Internal Medicine and are completing a three-year program in Gastroenterology.

Since 2010, I have served as the Associate Director of the Vanderbilt University Digestive Disease Research Center (VDDRC) and the Director of the Pilot and Feasibility Grant Program within the Center. The VDDRC is one of about 15 of such centers in the country, which are funded by the National Institutes of Health on a highly competitive basis. In 2015, I was asked to develop and lead a new research center at Vanderbilt, which I named the Vanderbilt Center for Mucosal Inflammation and Cancer.

Expertise in Mucosal Immunology and Inflammation: I have an international reputation as an expert in gastrointestinal mucosal immunology, inflammation, and carcinogenesis (cancer development). As of this writing I have published 139 papers, of which 121 are original research articles and 17 are reviews. I have also authored 3 book chapters and 168 research abstracts selected for presentation at national and/or international meetings. I have been continuously funded by the National Institutes of Health (NIH) as a Principal Investigator since 1996, and by the Department of Veterans Affairs since 1999. I have also held grants from the CCFA as research fellow, career development awardee, and as a senior researcher. I currently hold five

active grants from the NIH and one from the VA, with a total award amount of approximately $1.9 million/year. My research program and academic accomplishments have been recognized by election to the American Society for Clinical Investigation, an honor society for physician scientists, and election as a Fellow of the American Gastroenterological Association. I have given invited research presentations at many international meetings, in countries that include: Germany, France, Italy, Austria, Spain, Turkey, Mexico, Costa Rica, Colombia, Chile, Brazil, and Japan. I have been a Visiting Professor at 12 medical centers in the USA. I have chaired many research sessions at scientific meetings in the USA and abroad. I was elected as the 2017 Vice-Chair and 2019 Chair of a highly selective Gordon Research Conference. My laboratory group has had more than 150 presentations at the annual Digestive Disease Week meeting of the American Gastroenterological Association.

My research is laboratory-based and from a disease standpoint, focuses on inflammatory bowel disease (ulcerative colitis and Crohn's disease) and gastric inflammation associated with *Helicobacter pylori* infection. Our studies include cell culture models and many rodent models of inflammation, and consistently involve translational studies utilizing human tissues and case series/patient cohorts. For example I have conducted NIH-funded studies involving patients with ulcerative colitis, Crohn's disease, and *H. pylori* infection that have been both cross-sectional and prospective in design. I am also on the admissions committee for the Vanderbilt University Masters of Science in Clinical Investigation and have mentored four gastroenterology fellows obtaining this degree. Furthermore, I am the Principal Investigator of an NIH Program Project Grant, valued at approximately $750,000 per year, which is investigating the etiology of gastric cancer and is primarily patient-based and includes extensive epidemiological components; I am also the Principal Investigator of an NIH R01 grant, valued at over $400,000 per year, which is a clinical trial being conducted in Latin America to assess the utility of a novel pharmacologic agent in the prevention of gastric disease progression that derived from preclinical and translational studies in my laboratory. Thus, I have extensive experience in clinical research including epidemiology, clinical trial design, and translational studies that makes me highly qualified to assess etiological aspects of gastrointestinal inflammation and injury.

Additional evidence of my leadership role in the field of gastrointestinal immunology and inflammation is that I have invited to serve on 38 different NIH grant review study section panels, including 15 times for the panel "Gastrointestinal Mucosal Pathobiology", which included a four-year term as a permanent member. The purview of that review panel predominantly includes mucosal immunology and inflammation that is disease-related. I have also reviewed research grants multiple times for the CCFA, including two separate three-year terms plus many ad hoc reviews; the Department of Veterans Affairs; and multiple agencies in the UK, Germany, and within the USA. I have served as a receiving editor (equivalent to Associate Editor) for *Oncogene* and am currently on the editorial board, where I have handled manuscripts related to gastrointestinal cancer. I am currently serving a five-year term as an Associate Editor for *Gastroenterology*, the highest ranked journal in the specialty. I am one of 15 such Editors and I supervise the editorial process for over 100 manuscripts per year. My area of expertise for the journal is mucosal immunology, inflammation, and associated carcinogenesis; the disease focus is inflammatory bowel disease and upper GI tract inflammation. Therefore, I am very experienced in assessing research related gastrointestinal inflammation.

Summary of Clinical Experience: After graduation from Harvard Medical School in 1986, my three-year residency in Internal Medicine at Case Western Reserve University Hospitals of Cleveland in Ohio was undertaken from 1986-1989, and I successfully obtained Certification in Internal Medicine from the American Board of Internal Medicine in 1989. Thus I have been in practice in the overall field of Internal Medicine for 27 years. I completed my clinical and

research fellowship in Gastroenterology from 1989-1993 at The University of Chicago Medical Center and successfully obtained Certification in Gastroenterology from the American Board of Internal Medicine in 1993. Thus, I have been in clinical practice as a Gastroenterologist for 24 years, and counting the training period have been working in the specialty for 28 years.

While I was faculty at the University of Maryland School of Medicine from 1993-2005, my clinical workload included one day per week of performing endoscopy at the Baltimore VA Medical Center; two to three months a year of inpatient service as an Attending Gastroenterologist at the Baltimore VAMC, which included endoscopy on all inpatients for the months of coverage; regular attending coverage of the Gastroenterology Fellow's Clinic at the Baltimore VAMC of 5-10 hours per month; and night and weekend on call duties that included about 6 weeks per year of call, consisting of endoscopy coverage plus rounding duties on the weekends for both the University of Maryland Medical Center and the Baltimore VAMC. Furthermore, from 2002 to 2005, I was the Chief of Gastroenterology at the VA Maryland Healthcare System, where I oversaw all of the operations of the inpatient and outpatient services, and the endoscopy unit, and was the supervisor of two physician assistants and one nurse practitioner.

My position at Vanderbilt University School of Medicine has more time protected for research, but I have continued to have one day per week of performing endoscopy at the Nashville VA Medical Center of the VA Tennessee Valley Healthcare System; and one month per year of inpatient service as an Attending Gastroenterologist at the Nashville VAMC. Over the past 24 years in my practice primarily in the VA system I take care of patients with all types of problems in our specialty, including diseases of the esophagus, stomach, small intestine, colon, liver, and pancreas. I have the opportunity to see all types of patients including many with acute and chronic diarrhea, inflammatory bowel disease, celiac disease, and various enteropathies. We have many patients with iron deficiency anemia in which ruling out celiac disease is a frequent occurrence. I routinely direct the evaluation of patients with diarrhea, so that we often seek the cause through assessment for possible medication-associated diarrhea, infections, inflammatory bowel disease, chronic pancreatitis, and others.

I estimate that I have performed over 10,000 endoscopies in my career, which include mostly esophagogastroduodenoscopy and colonoscopy, the two procedures that Ms. Sutton underwent. I also have substantial experience in percutaneous endoscopic gastrostomy tube placement, esophageal dilatation, banding and sclerotherapy of esophageal varices, biopsy and polypectomy, and interventions for gastrointestinal bleeding. I am completely familiar with proper procedures and standard of care for performing endoscopy. I also am expert at reviewing reports of histopathology (slides from gastrointestinal tissues obtained by endoscopic biopsy as well as from surgical resections), and in examining the slides myself under the microscope. Because of my research involving a very large amount of histopathology, I have special interest in this area.

In addition I served as the Gastroenterology Fellowship Program Director for Vanderbilt University from 2005 to 2015. Thus I attended the vast majority of all of our teaching conferences and maintained a strong clinical exposure, as I was responsible for the clinical training experience of our fellows. I hold active clinical privileges at both Vanderbilt University Medical Center and the VA Tennessee Valley Healthcare System. The Department of Medicine requires that we obtain at least 100 hours of continuing medical education credits every two years, which exceeds the Tennessee state requirement of 40 hours/two years for licensure. This primarily obtained from the Medical Grand Rounds, Gastroenterology Grand Rounds, and Gastroenterology clinical case conference. I have attended the annual meeting of the American Gastroenterological Association (Digestive Disease Week) every year for the past 26 years. The

latest research and state-of-the art clinical recommendations are presented each year over a four-day period. I also attend several other national or international meetings a year that include clinical updates. I also attend and often serve as a moderator of a session at the annual Vanderbilt University CME Update Course in Gastroenterology. I have recertified my Gastroenterology Boards every ten years, as required, in 2003 and 2013, after my initial certification in 1993. This involved extensive self-study through the ABIM required modules and my study of review materials from the American Gastroenterological Association, online textbooks, fellow's review courses, and other online resources such as primary clinical reviews, guidelines, and more detailed clinical research articles.

I also have extensive teaching experience. While I was at University of Maryland I taught in the small group teaching modules in both the first and second year courses (physiology and pathophysiology), which included all areas of Gastroenterology, and for the last four years there I gave a lecture to the second year medical school class on disorders of the stomach and small intestine, which included malabsorption and diarrhea, and wrote the exam questions on these topics. I frequently had medical students round with me, in addition to Internal Medicine Residents and Gastroenterology Fellows. At Vanderbilt, I always have a Gastroenterology Fellow working with me on the Inpatient Consult Service at the Nashville VA, where I am supervising that trainee one-on-one during the entire time that I am performing my Attending coverage. I also work on some occasions with Internal Medicine Residents and Medical Students in the inpatient units and the endoscopy unit. I have also taught Surgical Residents how to perform endoscopy. For the last several years, I have worked with Vanderbilt University undergraduate students who shadow me as part of their premed honor society experience. Over the past 24 years as a faculty member, I have trained many medical students, residents, and Gastroenterology fellows in clinical and basic research. For the past five years I have directed the Digestive Disease Research component of an NIH-funded summer research program at Vanderbilt for medical students that come from around the USA. I select the students for the program, arrange their mentorship, and run research and clinical teaching sessions for them. I have also trained many postdoctoral research fellows, graduate students, and mentored more than 15 junior faculty in clinical and basic research.

Other cases in which, during the previous four years, the witness testified as an expert at trial or by deposition:

None.

Statement of the compensation to be paid for the study and testimony in the case:

I am compensated at the rate of $500 per hour for reviewing medical records, medical literature, and drafting this report.

Signature:

Keith T. Wilson, MD
January 30, 2017

Materials Reviewed:

Each of the references below has been carefully reviewed. I have also reviewed the report of Dr. Tackett.

I have also accessed online resources that include:

1. UpToDate.
2. Sleisinger & Fordtran's Gastrointestinal and Liver Disease.

References:

1. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, et al. (2012). Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 87: 732-8. PMC: 3538487.
2. Rubio-Tapia A, Talley NJ, Gurudu SR, Wu TT, Murray JA (2010). Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol*. 8: 344-9 e3. PMC: 3493150.
3. Cartee AK, Murray JA (2014). Sprue-like Enteropathy Associated with Olmesartan. *Curr Cardiovasc Risk Rep*. 8: 420. PMC:
4. Theophile H, David XR, Miremont-Salame G, Haramburu F (2014). Five cases of sprue-like enteropathy in patients treated by olmesartan. *Dig Liver Dis*. 46: 465-9. PMC:
5. Marthey L, Cadiot G, Seksik P, Pouderoux P, Lacroute J, Skinazi F, et al. (2014). Olmesartan-associated enteropathy: results of a national survey. *Aliment Pharmacol Ther*. 40: 1103-9. PMC:
6. Brown IS, Bettington A, Bettington M, Rosty C (2016). Self-limited coeliac-like enteropathy: a series of 18 cases highlighting another coeliac disease mimic. *Histopathology*. 68: 254-61. PMC:
7. Glass RI, Parashar UD, Estes MK (2009). Norovirus gastroenteritis. *N Engl J Med*. 361: 1776-85. PMC: 3880795.
8. Menne J, Haller H (2012). Olmesartan and intestinal adverse effects in the ROADMAP study. *Mayo Clin Proc*. 87: 1230-1; author reply 2. PMC: 3547579.
9. DeGaetani M, Tennyson CA, Lebwohl B, Lewis SK, Abu Daya H, Arguelles-Grande C, et al. (2013). Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. *Am J Gastroenterol*. 108: 647-53. PMC:
10. Greywoode R, Braunstein ED, Arguelles-Grande C, Green PH, Lebwohl B (2014). Olmesartan, other antihypertensives, and chronic diarrhea among patients undergoing

endoscopic procedures: a case-control study. *Mayo Clin Proc*. 89: 1239-43. PMC: 4157109.

11. Lagana SM, Braunstein ED, Arguelles-Grande C, Bhagat G, Green PH, Lebwohl B (2015). Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers. *J Clin Pathol*. 68: 29-32. PMC:
12. Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F, et al. (2016). Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 65: 1664-9. PMC:
13. Padwal R, Lin M, Etminan M, Eurich DT (2014). Comparative effectiveness of olmesartan and other angiotensin receptor blockers in diabetes mellitus: retrospective cohort study. *Hypertension*. 63: 977-83. PMC:
14. Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, et al. (2015). Immunopathogenesis of olmesartan-associated enteropathy. *Aliment Pharmacol Ther*. 42: 1303-14. PMC: 4626300.
15. Nagib MM, Tadros MG, ElSayed MI, Khalifa AE (2013). Anti-inflammatory and anti-oxidant activities of olmesartan medoxomil ameliorate experimental colitis in rats. *Toxicol Appl Pharmacol*. 271: 106-13. PMC:
16. de Araujo AA, Borba PB, de Souza FH, Nogueira AC, Saldanha TS, Araujo TE, et al. (2015). In a methotrexate-induced model of intestinal mucositis, olmesartan reduced inflammation and induced enteropathy characterized by severe diarrhea, weight loss, and reduced sucrose activity. *Biol Pharm Bull*. 38: 746-52. PMC:
17. de Araujo RF, Jr., Reinaldo MP, Brito GA, Cavalcanti Pde F, Freire MA, de Medeiros CA, et al. (2014). Olmesartan decreased levels of IL-1beta and TNF-alpha, down-regulated MMP-2, MMP-9, COX-2, RANK/RANKL and up-regulated SOCs-1 in an intestinal mucositis model. *PLoS One*. 9: e114923. PMC: 4273993.
18. Fatima D, Shaza A, Ahmad A-M (2016). Ameliorative effect of olmesartan medoximil on acetic acid induced colitis in rats. *Int J Pharm Clin Res*. 8: 604-9. PMC:
19. Sipal S, Halici Z, Kiki I, Polat B, Albayrak A, Albayrak F, et al. (2012). Comparative study of three angiotensin II type 1 receptor antagonists in preventing liver fibrosis in diabetic rats: stereology, histopathology, and electron microscopy. *Journal of molecular histology*. 43: 723-35. PMC:
20. Seko Y (2006). Effect of the angiotensin II receptor blocker olmesartan on the development of murine acute myocarditis caused by coxsackievirus B3. *Clin Sci (Lond)*. 110: 379-86. PMC:
21. Wu L, Mei L, Chong L, Huang Y, Li Y, Chu M, et al. (2016). Olmesartan ameliorates pressure overload-induced cardiac remodeling through inhibition of TAK1/p38 signaling in mice. *Life Sci*. 145: 121-6. PMC:
22. Schunemann H, Hill S, Guyatt G, Akl EA, Ahmed F (2011). The GRADE approach and Bradford Hill's criteria for causation. *J Epidemiol Community Health*. 65: 392-5. PMC:
23. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. (2004). Grading quality of evidence and strength of recommendations. *BMJ*. 328: 1490. PMC: 428525.
24. Aziz I, Peerally MF, Barnes JH, Kandasamy V, Whiteley JC, Partridge D, et al. (2016). The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015). *Gut*. PMC: